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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/690,115 | 10/21/2003 | Richard L. Apodaca | PRD2033NP | 3740 |

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| EXAMINER | |
|---|---|
| COLEMAN, BRENDA LIBBY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1624 | |

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/690,115 | APODACA ET AL. | |
| | Examiner | Art Unit | |
| | Brenda L. Coleman | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4 and 6-55* is/are pending in the application.

4a) Of the above claim(s) *47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-46 and 51-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04; 5/04; 8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-4 and 6-55 are pending in the application.

### *Election/Restrictions*

1. Applicant's election with traverse of Group I in the reply filed on March 16, 2006 is acknowledged. The traversal is on the ground(s) that it would not be a burden on the Examiner to examine all of the Groups together. This is not found persuasive because first a compound of formula (I) where n is 1 or 2 are clearly structurally dissimilar compounds which are classified in various subclasses under classes 540 and 544.

(1) Note MPEP 2173.05(h) "where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression. Therefore, what should be considered for patentable distinctness is the compound as a whole. Would a whole compound where n is 1, be patentably distinct from a whole compound where n is 2? If a reference for one would not be a reference for the other, then restriction is considered proper. Community of properties is not enough to keep a substituted piperazine in the same Markush claim, where the Markush expression is applied only to a portion of a chemical compound. It is the compound as a whole where instant n is 1 that must be considered for patentable distinctness.

Thus, separate searches in the literature would be required. However, should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if

the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

(2) The degree of burden on the examiner is high. The class/subclass search on the elected invention where n is 1 in the compounds of formula I would be as follows: class 514, subclasses 217.05, 227.8, 235.8, 252.11, 253.01, 253.05, 254.01 and 255.01; class 540, subclass 597 and class 544, subclasses 60, 121, 257, 360, 363, 372 and 391 which involved 8033 US patents. The classes and subclass mentioned above represent only the degree of burden within the U.S. Patent Classification System this does not include the search required in the prior art of journal articles and foreign patents.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 47-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 16, 2006.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 42-46 and 51-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The scope of

the method claims is not adequately enabled solely based on histamine $H_3$ receptor activity provided in the specification.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the instant invention has claims, which embrace substituted piperazine compounds.

HOW TO USE: Claims 44-46 and 51-55 are to a method for treating any and all diseases and/or conditions associated histamine $H_3$ receptor activity. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of claims 44-46 and 51-55 includes diseases and/or conditions not even known at this time, which may be associated with histamine $H_3$ receptor activity. While the treatment of allergic rhinitis have been linked with histamine $H_3$ receptor activity the art does not recognize use of such inhibitors as broad based drugs for treating all disorders instantly embraced.

It is difficult to treat many of the disorders claimed herein. Instant claim language embraces disorders not only for treatment but the **prevention**, which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop upper airway allergic response, itch, nasal congestion or allergic rhinitis, etc. There is no evidence of record,

which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders claimed herein.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art. See *In re Ruskin*, 148 USPQ 221; *Ex parte Jovanovics*, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. *Genentech Inc. v. Novo Nordisk* 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 2-4, 6-46 and 51-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following rejections apply:

a) Claims 2-4, 6-46 and 51-55 recite the limitation "compound" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

b) Claim 13 is vague and indefinite in that it is not known what is meant by claim1.

c) Claim 15 is vague and indefinite in that it does not end with a period indicating the end of the claim.

d) Claim 27 recites the limitation "cyano" in the definition of the substituents of $R^9$. There is insufficient antecedent basis for this limitation in the claim.

e) Claim 28 recites the limitation "(imidazolyl)$C_{1-6}$ alkylene" in the definition of the substituents of $R^9$. There is insufficient antecedent basis for this limitation in the claim.

f) Claim 28 recites the limitation "(tetrazolyl)$C_{1-6}$ alkylene" in the definition of the substituents of $R^9$. There is insufficient antecedent basis for this limitation in the claim.

g) Claim 28 recites the limitation "(triazolyl)$C_{1-6}$ alkylene" in the definition of the substituents of $R^9$. There is insufficient antecedent basis for this limitation in the claim.

h) Claim 28 recites the limitation "(pyrrolyl)$C_{1-6}$ alkylene" in the definition of the substituents of $R^9$. There is insufficient antecedent basis for this limitation in the claim.

i) Claims 44-45 and 55 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by histamine $H_3$ receptor inhibition. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in neurodegenerative disorders and allergic immunologic, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 6-10, 21, 42-46 and 51-55 are rejected under 35 U.S.C. 102(b) as being anticipated by MUTSUKADO et al, EP 0 186 817. MATSUKADO teaches the compounds, compositions and method of use of the compounds of formula I where $R^1$ is methyl or ethyl; $R^2$ and $R^3$ are H; X is O; ad $R^4$ is [[5-chloro-1-(1,1-dimethylethyl)-1,6-dihydro-6-oxo-4-pyridazinyl]amino]methyl as shown on page 65, examples 41 and 42.

6. Claims 1, 2, 6-10, 12-15, 18, 31, 35-38, 42-46 and 51-55 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention. By the applicants own admission the compound of example 43 was on sale more than one year prior to the date of application for patent in the United States.

An issue of public use or on sale activity has been raised in this application. In order for the examiner to properly consider patentability of the claimed invention under 35 U.S.C. 102(b), additional information regarding this issue is required as follows: It is requested that information regarding the sale of the compound of example 43 be provided to the Examiner for proper consideration.

Applicant is reminded that failure to fully reply to this requirement for information will result in a holding of abandonment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brenda Coleman

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Primary Examiner Art Unit 1624
May 30, 2006

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